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EDITORIAL

Of laminins and delamination in Alport syndrome

Alport syndrome is a genetic disease of the glomerular basement membrane (GBM) leading to a delayed-onset, progressive nephritis. Alport syndrome is caused by mutation in any one of the three genes encoding the type IV collagen α3, α4, and α5 chains, *COL4A3*, *COL4A4*, and *COL4A5*, respectively. These three chains form the major collagen IV network that is present in the GBM. Most mutations that cause Alport syndrome result in the absence of all three of these collagen IV chains, presumably because their assembly into the GBM requires the presence of all three chains [1, 2].

Alport GBM is able to function normally early in life because the collagen α1 and α2(IV) chains substitute for the missing α3-α5(IV) chains. However, there is a progressive thickening and splitting of Alport GBM that is associated with the onset of hematuria and eventual glomerular obsolescence. Why these very characteristic ultrastructural GBM abnormalities occur is an important question with regard to onset and progression of the disease. Three major theories have emerged. First, intrinsic properties of the collagen α1/α2(IV) network in Alport GBM makes the GBM less structurally sound and more susceptible to mechanical strain caused by the pressure of ultrafiltration. Second, the collagen α1/α2(IV) network is more susceptible to proteolysis by endogenous proteases than is the normal α3α4α5(IV) network [3]. Third, replacement of the normal collagen IV network with the α1/α2(IV) network results in aberrant accumulation of noncollagenous extracellular matrix molecules, leading eventually to a disrupted ultrastructure.

In support of the first two theories, the collagen α3 and α4(IV) chains contain significantly more cysteines than do the α1 and α2(IV) chains, so more extensive disulphide cross-linking, both within and between trimers, should occur [4]. This would be expected to impart increased mechanical stability to the collagen IV network and perhaps also resistance to proteases. Indeed, in vitro studies showed that a bulk basement membrane preparation from an Alport syndrome kidney was more susceptible to protease degradation than was a similar preparation from a normal kidney [3]. However, whether this reflects the in vivo situation with respect to the GBM remains to be determined.

In support of the third theory, ectopic accumulation of the laminin α2 and β1 chains in the GBM occurs both in human Alport syndrome and in animal models of Alport syndrome [5–7]. In addition, we found ectopic accumulation of laminin α1 in mouse Alport GBM [6]. Normally, laminin-11 (α5β2γ1) is the only known laminin trimer present in the mature GBM [8]. Accumulation of the laminin α2, β1, and α1 chains could be pathogenic, perhaps leading to the typical lesions observed in Alport GBM and/or to aberrant behavior of the adjacent podocytes and subsequent foot process effacement and proteinuria. Expression of laminins α1 and β1 is particularly interesting because these two chains are found in developing GBM, but they are normally eliminated at maturity; α1 is replaced by α5 and β1 is replaced by β2 [9].

In this issue of *Kidney International*, Abrahamson et al [10] present a detailed analysis of laminin α1 and β1 deposition in the GBMs of a mouse model of Alport syndrome harboring a *Col4a3* mutation. In addition to confirming the finding that laminins α1 and β1 are deposited in Alport GBM, they show that in still developing kidneys, laminin α1 is eliminated on schedule at the capillary loop stage of glomerulogenesis, but it reappears in the mature GBM very soon thereafter. The sites of reappearance are those areas of GBM that exhibit the subepithelial thickening and delamination that is characteristic of Alport GBM. The authors elegantly show by immunoelectron microscopy that both podocytes and endothelial cells contribute laminin α1 to the affected GBM. Interestingly, no α1 or β1 was detected in ultrastructurally normal stretches of GBM, demonstrating a clear association between GBM lesions and deposition of ectopic laminins.

Like all provocative findings, these lead to additional important questions that will hopefully be answered by future studies. First, do the GBM lesions elicit synthesis of the ectopic laminins by the adjacent glomerular cells, or does the aberrant type IV collagen complement present in Alport GBM elicit deposition of ectopic laminins, which then results in the observed lesions? If the latter is correct, then preventing ectopic expression of the laminin α1, β1, and α2 chains will perhaps improve GBM ultrastructure and slow disease progression. In fact, mutation of integrin α_1 in the same mouse model of Alport syndrome inhibited both accumulation of ectopic laminins (α2 and β1) and GBM delamination, and this was associated with slowed progression to renal failure [5]. (Whether α1 deposition was affected in this context was not studied.) Second, are the ectopic laminins themselves pathogenic, or are the GBM lesions alone sufficiently

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disruptive to either ultrafiltration or podocyte homeostasis so as to cause foot process effacement and disease? While laminins α2 and β1 are widely expressed, laminin α1 is a relatively rare chain in tissues other than kidney [11], and in nephrons it is normally confined primarily to basement membranes of the proximal tubule and loop of Henle [8]. The restricted expression pattern of laminin α1 may suggest that it confers unique properties that are not compatible with some specialized basement membrane functions, such as those associated with glomerular ultrafiltration. This would be consistent with the abrupt elimination of laminin α1 from the developing GBM before the onset of significant glomerular capillary blood flow and ultrafiltration. A better understanding of both the mechanism of the reexpression of laminin α1 associated with Alport syndrome and its biological consequences is certain to provide important new insights into diverse glomerulopathies and GBM homeostasis.

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REFERENCES

1. Kashtan CE: Alport syndrome. *Kidney Int* 51 (Suppl 58):S-69–S-71, 1997
2. Hudson BG, Reeders ST, Tryggvason K: Type IV collagen: Structure, gene organization, and role in human diseases. *J Biol Chem* 268:26033–26036, 1993
3. Kalluri R, Shield CF, III, Todd P, *et al*: Isoform switching of type IV collagen is developmentally arrested in X-linked Alport syndrome leading to increased susceptibility of renal basement membranes to endoproteolysis. *J Clin Invest* 99:2470–2478, 1997
4. Zhou J, Reeders ST: The α chains of type IV collagen. *Contrib Nephrol* 117:80–104, 1996
5. Cosgrove D, Rodgers K, Meehan D, *et al*: Integrin alpha$_1$beta$_1$ and transforming growth factor-beta1 play distinct roles in Alport glomerular pathogenesis and serve as dual targets for metabolic therapy. *Am J Pathol* 157:1649–1659, 2000
6. Kashtan CE, Kim Y, Lees GE, *et al*: Abnormal glomerular basement membrane laminins in murine, canine and human Alport syndrome: Aberrant laminin alpha2 deposition is species-independent. *J Am Soc Nephrol* 12:252–260, 2001
7. Andrews KL, Mudd JL, Li C, Miner JH: Quantitative trait loci influence renal disease progression in a mouse model of Alport syndrome. *Am J Pathol* 160:721–730, 2002
8. Miner JH: Renal basement membrane components. *Kidney Int* 56:2016–2024, 1999
9. Miner JH: Developmental biology of glomerular basement membrane components. *Curr Opin Nephrol Hypertens* 7:13–19, 1998
10. Abrahamson DR, Prettyman AC, Robert B, St. John PL: Laminin-1 reexpression in Alport mouse glomerular basement membranes. *Kidney Int* 63:826–834, 2003
11. Virtanen I, Gullberg D, Rissanen J, *et al*: Laminin alpha1-chain shows a restricted distribution in epithelial basement membranes of fetal and adult human tissues. *Exp Cell Res* 257:298–309, 2000